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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,088	09/12/2003	Andrew Vaillant	029849-0206	6597

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,088	VAILLANT ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March14, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The Office acknowledges the receipt of Applicant's restriction election, filed on March 14, 2006. Applicant elects Group II, claims 3 and 11-32 for prosecution. Applicant also elects the species of the oligonucleotide REP 2006, phosphorothioate linkage and 2'-O-methyl modification to the ribose moiety. In addition, the Applicant wishs to specify that the elected oligonucleotide is a monomer. The applicant also elects the specie consisting of an antiviral pharmaceutical composition adapted for delivery by injection. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

2. The Examiner acknowledges that dependent claims 4-10 were overlooked and should be included in Group II.

3. Accordingly, claims 1-38 are pending. Claims 1, 2 and 33-38 are withdrawn as non-elected. Claims 3-32 are under the examination in the instant Office action.

Specification

4. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

Information Disclosure Statement

5. The information disclosure statement submitted on November 26, 2004 is in compliance

with the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 3-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detail chemical structure of the encompassed genus of undefined nucleotide fragment, proteins or polypeptides. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Lid.*, 18 USPQ2d 1016.
>
> Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved

> until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).
>
> A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

8. Claims 3-32 are drawn to an anti-HBV pharmaceutical composition comprising a library of randomer oligonucleotides wherein said randomer oligonucleotides are at least 10 nucleotides in length, wherein said randomer oligonucleotides at least 40 nucleotides in length, wherein said oligonucleotides are 40 nucleotides in length (REP 2006), wherein said randomer oligonucleotides have phosphorothioate linkage and 2'-O-methyl modification to the ribose moiety, wherein said oligonucleotide occurs principally by a non-sequence complementary mode of action.

9. Since the structural limitation to the claimed randomer oligonucleotides is only minimal length, the scope of claims 3-32 encompasses all possible randomer oligonucleotides that are more than 10 nucleotides in length. The possible variations are enormous to such randomer oligonucleotides longer than 10 or 40 nucleotides in the claimed pharmaceutical composition. While having written description of a few randomer oligonucleotides identified in the specification figures and/or examples, the specification has not disclosed sufficient species of randomer oligonucleotides longer than 10 or 40 nucleotides with phosphorothioate linkage and 2'-O-methyl modification to the ribose moiety. Consequently, there is no indication that

Applicant was in possession of all randomer oligonucleotides that are more than 10 nucleotides long and with phosphorothioate linkage and 2'-O-methyl modification to the ribose moiety as broadly claimed.

10. Claims 3-32 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught

one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

12. Claims 3-32 are drawn to a pharmaceutical composition comprising a library of randomer oligonucleotides that are at least 10 or 40 nucleotides in length for prevention and treatment of HBV infection. The nature of pharmaceutical arts is that it involves screening both in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities, providing clinical benefit. In the instant case, while Applicant has shown that some randomer oligonucleotides can inhibit DHBV in cell culture, the specification has not disclosed that such randomer oligonucleotides can inhibit HBV in vivo. Those of skill in the art recognize that in vitro assays are generally useful to observe basic physiological and cellular phenomenon, such as a virus-cell interaction. However, the correlation of the physiological condition in vivo is generally lacking. Variables such as target accessibility and biological stability, half-life or rate of clearance from the blood are important parameters for oligonucleotide-based drugs in achieving their efficacy in vivo. Hence, in the absence of evidence showing a correlation of anti-HBV activities of claimed randomer oligonucleotides in vitro with efficacy in vivo, one of skill in the art is unable to fully predict possible results of clinical benefit of such randomer oligonucleotides only based on the results from cell culture results.

13. The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification (see MPEP 2164.05(a) [R-2]). *In re Fisher*, 427 F.2d 833,166

USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The instant specification has not provided any working examples to teach the claimed compositions would inhibit HBV replication *in vivo*. Although individuals of the skill in the art is high, it takes **undue** amount of experimentation to evaluate whether or not the claimed randomer oligonucleotides can provide clinical benefit as an antiviral pharmaceutical composition for treating HBV infection.

14. Moreover, in order for the full breadth of the invention to be enabled, a skilled artisan would have to develop a method to deliver claimed randomer oligonucleotides to target cells in vivo. Although Applicant has suggested in the specification to delivery the randomer oligonucleotide by using a delivery system, the state of the prior art has illustrated that the current delivery technology in the art is not sufficient to delivery oligonucleotide-based drugs to their targets in vivo. (Opalinska, 2002). The specification has not provided any specific teachings regarding how to deliver such randomer oligonucleotides into target calls in vivo and how to maintain effective concentration in vivo at therapeutic levels to inhibiting multiplication of viral genomes during HBV replication. Because of the limitations of current gene delivery technology in the art and lack of guidance in the specification, it would require an **undue** quantity of necessary experimentation by one skilled in the art to develop a method to deliver claimed randomer oligonucleotides in to target cells in vivo before using the instant invention.

15. Since the scope of claims 3-32 clearly covers a very broad application of an anti-HBV pharmaceutical composition in human, in view of the empirical and unpredictable nature of anti-viral drug development, and lack of guidance and working examples in the specification, one skilled in the art cannot practice the claimed invention without undue experimentation.

Therefore, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 3-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 18-26 of copending Application No. 10/661,403. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a same process using the same products.

18. The instant claims 3-32 are drawn to an anti-HBV pharmaceutical composition comprising a therapeutically effective amount of at least one pharmacologically acceptable, wherein the antiviral oligonucleotide at least 10 nucleotides in length, wherein the antiviral

oligonucleotide at least 40 nucleotides in length, wherein the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action.

19. Claims 1-15 and 18-26 of copending Application No. 10/661,403 claim an antiviral random oligonucleotide, wherein the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action, wherein said oligonucleotide is at least 29 nucleotides in length and the sequence of said oligonucleotide is not complementary to any portion of the genomic sequence of said target virus, wherein said oligonucleotide targets a DNA virus, wherein said oligonucleotide targets a RNA virus.

20. Since the claim limitations of 10/661,403 clearly cover all DNA and RNA viruses, HBV, which is a DNA virus, is a species of the genus in the claims of co-pending application 10/661,403. The pharmaceutical compositions that can target all DNA viruses encompass the pharmaceutical composition against HBV. The anti-HBV pharmaceutical compositions (species) of instant claims will anticipate the anti-DNA virus composition (genus) in the copending case.

21. Claims 3-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-51 of copending Application No. 10/661,402, over claims 3-32 of copending Application No. 10/661,415, and over claims 23-52 of copending Application No. 10/969,812. Although the conflicting claims are not identical, they are not patentably distinct from each other because these 4 sets of claims are drawn to same pharmaceutical compositions.

22. Claims 22-51 of 10/661,402 are directed to an antiviral pharmaceutical composition comprising a therapeutically effective amount of at least one pharmacologically acceptable,

antiviral oligonucleotide at least 10 nucleotides in length, wherein said composition is approved for use in humans against a target virus, and the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action, and said target virus is different from HIV-1, HIV-2, HSV-1, HSV-2, CMV, RSV, parainfluenza virus, and HBV; and a pharmaceutically acceptable carrier.

23. Claims 3-32 of 10/661,415 are directed to an antiviral pharmaceutical composition comprising a therapeutically effective amount of at least one pharmacologically acceptable, antiviral oligonucleotide at least 10 nucleotides in length, wherein said composition is approved for use in humans against RSV or parainfluenza virus and the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action; and a pharmaceutically acceptable carrier.

24. Claims 23-52 of 10/969,812 are directed to An antiviral pharmaceutical composition comprising a therapeutically effective amount of at least one pharmacologically acceptable, antiviral oligonucleotide at least 10 nucleotides in length, wherein said composition is approved for use in humans against a target virus, and the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action, and said target virus is different from HIV-1, HIV-2, HSV-1, HSV-2, CMV, RSV, parainfluenza virus, and HBV; and a pharmaceutically acceptable carrier.

25. These four sets of claims are not patentably distinct from each other because they are drawn to same pharmaceutical compositions for following reasons: First, the claimed anti-HBV pharmaceutical composition of the instant application comprising a library of random oligonucleotides that encompasses all possible randomer oligonucleotides more than 10

nucleotides in length. The structural limitations to the claimed library of randomer oligonucleotides of the instant application are same as those libraries of randomer oligonuckleotides of other copending applications. Secondly, the instant specification has never identified, isolated or disclosed any specific randomer oligonucleotides that specifically against HBV from the library of random oligonucleotides that are at least 10 nucleotides in length. Although randomer oligonucleotides are made using random nucleosides, the nucleotides that inhibit HBV should have their own specific identities, which are their specific sequences. Applicant has not disclosed any specific randomer oligonucleotides specifically against HBV. In stand, Application claims entire library of randomer oligonucleotides more than 10 nucleotides in length, in which the majority of randomer are not anti-HBV-specific. Thirdly, Applicant has not disclosed any specific randomer oligonucleotides that specifically inhibit RSV or parainfluenza virus in 10/661,415, nor those that specifically against any virus different from HIV, HSV, CMV, RSV, parainfluenza virus, and HBV in both 10/661, 402 and 10/989, 812. In stand, Applicant claims entire libraries of randomer oligonucleotides, in which the majority of randomers are not any virus specific. Since the structural limitations to all claimed libraries of randomer oligonucleotides are same in the instant application, copending Applications 10/661,402, 10/661,415, and 10/969,812, and all these libraries are not any virus specific, the anti-HBV pharmaceutical composition comprising a library of randomer oligonucleotides is SAME pharmarceutical compositions as those against other viruses in copending Applications 10/661,402, 10/661,415, and 10/969,812.

26. These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Remarks

27. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

BP

Bo Peng, Ph.D.
April 27, 2006

JEFFREY STUCKER
PRIMARY EXAMINER

Opalinska J. "Nucleic acid therapeutics: Basic principles and recent applications" *Nature Reviews Drug Discovery*, Vol. 1 (2002), pages 503-514.